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Division of Dockets Management (HFA-305)
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Re: Comments to the Docket on 21 CFR Part 11
Docket No. 2004N-0133

- Three patients die of radiation overdose due to software design flaws
- One patient dies due to a software logic error in an infusion pump
- Five patients die of radiation overdose because the software allowed lethal data entry errors
- The status of 8,500 hospital patients is switched from “discharged” to “deceased” due to faulty software database conversion

The first three incidents listed above are tragic examples of the worst possible result of defective software. The last incident, in which no patients were harmed, would be humorous – if not for the fact that it represents one of the most common software errors – one that often results in far more serious consequences and which can easily go undetected without proper controls.

The tremendous advantages that computerization brings to all areas of FDA-regulated activity are undeniable. With that incredible speed and power, though, comes the potential to quickly and easily propagate errors to hundreds or thousands of records, in a manner that is virtually inconceivable in the paper world. It is for this reason that FDA must clearly define and enforce a minimally acceptable level of software controls and requirements for electronic records, electronic signatures, and computerized systems in general, where the public health and safety are at risk.

FDA took a bold step toward implementing such regulations with the issuance of Part 11 in 1997. Unfortunately, as we all know today, certain provisions – and, more accurately, certain interpretations – of Part 11 were “over the top” and pushed the envelope beyond what was reasonable and necessary to ensure the integrity, reliability, and trustworthiness of regulated records. The resultant backlash has led FDA to retreat from many key Part 11 provisions in the form of the Scope and Application guidance while re-examining the regulation for possible changes.

We applaud FDA’s efforts to make Part 11 a better and more practical regulation. We oppose any attempt to rescind Part 11 or to dilute it to such a degree that it might as well be rescinded. The “80/20” rule is definitely applicable to Part 11 and its preamble. At least 80% (if not more) of Part 11’s original provisions represent

sound data security and integrity requirements, practices and procedures that should be integral to any applications and records that may ultimately impact the public health. To remove this baseline of requirements would represent a step backwards – especially in light of the overwhelming wave of similar requirements found in other regulations, including HIPAA and Sarbanes-Oxley.

The argument has been made that Part 11 is superfluous because of the predicate rules. With the exception of the Quality System Regulation (21 CFR 820), this argument is without merit. While the GLPs have at least a few important software and system requirements, the drug GMPs have far less, and the GCPs are virtually silent on the subject. It should be recognized that most predicate rules were not crafted with electronic records and signatures in mind, and thus fall short of what is need to ensure the integrity and reliability of these systems.

The attached recommendations do not address all of the questions raised by FDA in the Federal Register notice published April 8, 2004. They do, however, represent the issues that we feel are most critical and which must be addressed in any Part 11 revision or additional guidance. We thank FDA for the opportunity to provide our comments, and we would be happy to provide additional information on any of the issues discussed herein.

Very truly yours,
SEC ASSOCIATES, INC.

John C. McKenney, Sr.
President and CEO

Comments to the Part 11 Docket (Docket No. 2004N-0133)

Line(s)[1]	Comment	Recommendation
N/A	In its re-examination of Part 11, FDA could benefit greatly from industry experience gained since Part 11 was enacted. This one-time submission of comments to the docket will not reap the benefits of live interaction and specific topic discussions.	FDA should convene an Expert Advisory Panel to advise them on next steps for possible Part 11 revisions.
38-42 **A.1.**[2]	As noted in our cover letter, the Part 11 Scope and Application Guidance shifts much of the compliance burden back on the predicate rules. However, most predicate rules were written before the widespread use of computerized systems in GxP operations. **Most predicate rules do not address important controls and safeguards needed to assure the integrity and trustworthiness of electronic record systems.** The Drug GMPs (211), GCPs, and to a large extent the GLPs (58), are lacking important controls and safeguards needed for electronic record systems. For example, the GCPs do not explicitly require validation of computer systems used in clinical trials. Reliance on the predicate rules, therefore, will fall short of what is needed to assure data and signature integrity and reliability. Furthermore, reliance on the predicate rules alone will result in widely varying interpretations by industry and FDA.	Long term: FDA should provide guidance documents, and consider revising the GCPs and drug GMPs to address computerized system and quality system requirements (analogous to the Quality System Regulation and "General Principles of Software Validation" guidance from CDRH). In the meantime, FDA should take an active role in educating industry on its predicate rule expectations for e-record systems. Short term: Consider reinstating certain Part 11 provisions set aside by the Scope guidance, with changes as appropriate. For example, reinstate the validation requirement (since it is absent from the GCP predicate rules), but allow for a risk-based approach to be used.
179-181 **D.2.**	Implied vs. Explicit record requirements: Many in industry assume that implied records are covered by Part 11. However, the Scope guidance and live comments by FDA personnel seem to indicate that FDA's intent is that only explicitly stated record requirements fall under Part 11. If the latter interpretation is correct, then many important implied records are exempt from Part 11, which runs counter to the very reasons for which Part 11 was created.	Rather than issuing a blanket exemption for implied records, require that firms take a risk-based approach to Part 11 controls for all regulatory records.

[1] Line numbers refer to the Final Scope and Application Guidance, August, 2003.
[2] The alphanumeric references correspond to the numbers in the FDA Federal Register announcement (Vo. 69, No. 68 / Thursday, April 8, 2004) regarding the public meeting that was originally scheduled for June 11, 2004.

Comments to the Part 11 Docket (Docket No. 2004N-0133)

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179-181 **D.2.**	Historically, FDA has held companies accountable for what is required by the company's SOPs. This includes records that the firm's SOPs require it to keep, even when such records are not required by predicate rules. In other words, FDA has treated a firm's SOPs with nearly the same weight as predicate rules. Lines 179-181 in the Scope guidance, however, seem to imply that records required by a firm's SOPs, but not by predicate rules, will not require compliance with Part 11.	Clearly state whether or not records required by a firm's SOPs, but not explicitly by predicate rule, must be Part 11 compliant if maintained and used electronically.
166-171 **A.1.**	As a result of the position stated in the referenced lines, **firms may rely on paper records in order to avoid the necessary controls and validation** of the underlying electronic record system that generated the paper. This may result in unwarranted confidence in the printed record, without having the proper controls and procedures necessary to assure the integrity of the data and signatures in the system that generated the printout. Appropriate controls and procedures must be applied to computerized systems and records, because the systems are often highly technical and complex; they are largely invisible to the user; and users often place considerable (and sometimes misplaced) trust and confidence in their output.	FDA should not inadvertently encourage firms to avoid important security and integrity controls by allowing them to rely (or appear to rely) on the printed output of critical systems. The information on the paper may be unreliable without appropriate Part 11 controls for the underlying computer system.
203-205 **No Direct Reference in F.R. notice**	The Scope guidance states that **records that make up a submission are not subject to Part 11 unless they are required by predicate rules**. This seems to be a gap that may allow for potentially significant data integrity problems in records that are used to provide conclusions and claims in a NDA. For instance, case histories are required by predicate rule. However, the clinical data management system and subsequent iterations of records created and manipulated to provide the tables and analyses in a NDA are not explicitly covered by predicate rules. To not require validation and appropriate Part 11 controls around these systems is an invitation to potential data integrity problems.	Because the current GCP predicate rules do not adequately address many of the systems that manipulate critical data in the submission life cycle, FDA should advocate a risk-based approach, requiring (at a minimum) a "justified and documented risk assessment and a determination of the potential of the system to affect [data] quality and safety and record integrity." This approach should be required for all systems that can affect quality, safety, and record integrity, regardless of whether or not a given system or record is explicitly addressed in the existing predicate regulations.

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B.1.	The Scope guidance defines a few specific Part 11 requirements for which a risk-based approach is permitted.	FDA should consider permitting a risk-based approach to all Part 11 provisions, including the electronic signature requirements. For example, operational system checks, device checks, and controls over systems documentation should all be risk-based. Similarly, some electronic systems are far more critical than others. The controls applied to those systems should be based on risk, rather than on a one-size-fits-all strategy.
General Comment	Part 11 requirements in large measure represent good information security and integrity practices. With all of the emphasis now on PAT, electronic submissions, electronic patient reported outcomes, and so on, the controls and procedures required by Part 11 are more important now than they were in 1997.	This is not the time to minimize Part 11. Rather, the focus should be on eliminating the extreme Part 11 requirements (or, more likely, extreme expectations and interpretations), while heavily emphasizing and reinforcing the sound technical and procedural requirements embodied in Part 11.
44-47 259-264 **D.6.**	Virtually all systems in operation before August 20, 1997, have undergone hardware, firmware, and/or software upgrades, leaving many of these systems substantially different from their pre-Part 11 state. The wording in the guidance, however, seems to imply that FDA will overlook any changes, regardless of how significant, in exempting pre-Part 11 systems. This view runs counter to FDA's stated goal of applying a risk- and science-based approach to GMP systems, since it disregards the potential for high-risk modifications and removes the requirement for scientific analysis that should be applied to the evaluation of system modifications.	Clarify the intent with respect to legacy systems. State that changes to legacy systems should be evaluated using a "justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety and record integrity (lines 208-209)." Require that the risk assessment be the determining factor in whether a legacy system should be brought into compliance with Part 11.

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218-220 **B.1.**	In order for FDA to enforce validation requirements, is it necessary for the predicate rule(s) to specifically use the word "validation"? Or, can FDA claim (and enforce) that validation is required in order to demonstrate compliance with record requirements such as "accurate and complete", or "accurate and adequate"? If the answer to the first question is "yes", then many critical record systems (such as most GCP record systems) will go unvalidated. On the other hand, if the answer to the second question is "yes", then we are left with a highly subjective approach for determining which record systems must be validated. Either scenario is flawed.	Ideal long-term solution: Update the GCPs, GLPs, and drug GMPs to explicitly state which records (or record systems) must be validated. This could be accomplished in a manner similar to that used in the Quality System Regulation section 820.70(i) which states, "When computers or automated data processing systems are used as part of production *or the quality system*, the manufacturer shall validate computer software for its intended use according to an established protocol." Short-term solution: Help industry understand FDA's expectations in this area through published guidance and public presentations.